

(19) World Intellectual Property Organization  
International Bureau(43) International Publication Date  
15 February 2001 (15.02.2001)

PCT

(10) International Publication Number  
WO 01/10409 A1

- (51) International Patent Classification<sup>7</sup>: A61K 9/08, 31/573, A61P 37/08 SUGIBAYASHI, Nobuya [JP/JP]: 4-4-13, Miyahara, Utsunomiya-shi, Tochigi 320-0835 (JP).
- (21) International Application Number: PCT/JP00/05200 (74) Agents: SUZUYE, Takehiko et al.; Suzuye & Suzuye, 7-2, Kasumigasaki 3-chome, Chiyoda-ku, Tokyo 100-0013 (JP).
- (22) International Filing Date: 3 August 2000 (03.08.2000)
- (25) Filing Language: English (81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.
- (26) Publication Language: English
- (30) Priority Data: 9918559.7 7 August 1999 (07.08.1999) GB (84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).
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- Published:**  
 — With international search report.  
 — Before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments.
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

(54) Title: AQUEOUS NASAL FORMULATION

(57) Abstract: The present invention provides an aqueous nasal formulation comprising beclomethasone dipropionate anhydride for use in the treatment of respiratory disorders.

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## 1

## DESCRIPTION

## AQUEOUS NASAL FORMULATION

The present invention relates to an aqueous nasal formulation for use in the treatment of respiratory disorders.

5

Aerosol formulations are commonly used as effective anti-inflammatory treatments, but have implications with environmental safety. The most commonly used propellants in such formulations were previously chlorofluorocarbon containing (or CFC) propellants, however, these are currently being phased out, following the 1987 Montreal Protocol Agreement.

10

Since then, safer hydrogen containing fluorocarbons have been used as propellants in aerosol formulations, but these are relatively expensive and the environmental impact of these new propellants has also been questioned.

15

Thus, there is a need for safe anti-inflammatory treatments such as aqueous nasal formulations. The corticosteroid beclomethasone dipropionate (9 $\alpha$ -chloro-16 $\beta$ -methyl-1,4-pregnadiene-11 $\beta$ , 17 $\alpha$ , 21-triol-3, 20-dione-17,  $\alpha$ 21-dipropionate) is well known as a topical anti-inflammatory steroid and is found in aqueous nasal formulations.

20

Prior aqueous nasal formulations containing beclomethasone dipropionate, used in treating such indications as allergic rhinitis (such as Beconase™ AQ) have utilised beclomethasone dipropionate monohydrate in addition to the following constituents:

25

Anhydrous dextrose;  
Avicel RC591 (Microcrystalline cellulose and  
carboxymethylcellulose sodium);  
Phenylethyl alcohol;  
Benzalkonium chloride;

30

Polyoxyethylene (20) sorbitan monooleate;  
and purified water

5 Beclomethasone dipropionate monohydrate is not currently licensed in all territories of the world (notably not in Japan) and as a consequence, nasal formulations containing such a medicament cannot be marketed in such territories without substantial research effort and expense. However, there is an alternative anhydrous form of beclomethasone dipropionate, previously used in a nasal formulation (eg. Aldecin™ AQ) which contains the following constituents:

10

Micronised beclomethasone dipropionate anhydrate;  
Avicel RC591 (Microcrystalline cellulose and  
carboxymethylcellulose sodium);

Glycerol;

15

Propylene glycol;  
Polyoxyethylene (20) sorbitan monooleate;  
and purified water.

20

However, in the absence of a sealed pressurised container, as with the propellant based delivery systems, these formulations may be prone to contamination. As a consequence, potentially harmful bacteria may contaminate the formulation and then be inhaled directly into the nasal cavity. Additionally, these formulations have also been known to cause irritancy, which is especially undesirable in respect of paediatric treatment.

25

Thus, according to the present invention we provide a pharmaceutical formulation which comprises an aqueous solution of carboxy methylcellulose sodium, glycerol, propylene glycol and polyoxyethylene (20) sorbitan monooleate, containing suspended therein particulate microcrystalline cellulose

and beclomethasone dipropionate anhydrate characterised in that said aqueous suspension further comprises:

- 5                   Dextrose;  
                  Phenylethyl alcohol;  
                  Benzalkonium chloride;  
                  Disodium hydrogen orthophosphate; and  
                  Citric acid

- 10   The presence of dextrose, disodium hydrogen orthophosphate and citric acid is intended to overcome the irritancy problems associated with current anhydrous beclomethasone dipropionate formulations. This improvement is believed to be mediated through the dextrose acting as an isotonicity adjusting agent. Furthermore, the beclomethasone dipropionate anhydrate may be stabilised by  
15   appropriate selection of pH using disodium hydrogen orthophosphate and citric acid to act as a buffer.

- In addition, phenylethylalcohol and benzalkonium chloride are present within the formulation to act as preservatives.

- 20                   Dextrose is preferably used as dextrose anhydrous. Disodium hydrogen orthophosphate is preferably used as disodium hydrogen orthophosphate anhydrous. Citric acid is preferably used as citric acid monohydrate. Microcrystalline cellulose and carboxy methylcellulose sodium is preferably used  
25   as the branded product Avicel RC591 (which typically contains 87-91% microcrystalline cellulose and 9 -13% carboxy methylcellulose sodium).

- Particulate beclomethasone dipropionate anhydrate will suitably be micronised and have a mean particle size less than 20 $\mu$ m, preferably less than 10 $\mu$ m,  
30   especially 1-5 $\mu$ m.

Particulate microcrystalline cellulose will preferably have a particle size in the range 1 to 100 $\mu$ m.

5 A pharmaceutically acceptable amount of micronised beclomethasone dipropionate anhydrate is present within the formulation, which is preferably between 0.025-0.25% (w/w), especially 0.1% (w/w). The branded product Avicel RC591 and propylene glycol are suspending agents and are desirably added in a suitable amount to achieve this function, preferably between 1-5% and 0.1-20% (w/w) respectively, especially 1.5% and 1.0% (w/w) respectively.

10

We believe that Avicel RC591 acts as a suspending agent by imparting thixotropic properties to the formulation, wherein the formulation may become a stable suspension upon being stirred, shaken or otherwise disturbed. We similarly believe that propylene glycol aids stabilisation of the formulation by  
15 reducing the bubbles which arise due to the presence of Avicel RC591 and benzalkonium chloride in the formulation.

Glycerol is added in a suitable amount to achieve its desired function as an excipient which reduces the solubility of beclomethasone dipropionate anhydrate in formulation; preferably the amount of glycerol will be such as to make the beclomethasone dipropionate anhydrate essentially insoluble in the formulation.  
20 An amount of glycerol which is preferably between 0.1-6% (w/w), especially 4.0% (w/w) will be suitable. The wetting agent, polyoxyethylene (20) sorbitan monooleate (typically supplied as the branded product Polysorbate 80) is  
25 desirably added in a sufficient quantity to achieve this function, preferably between 0.001-0.01% (w/w), especially 0.007% (w/w). The components disodium hydrogen orthophosphate anhydrous and citric acid monohydrate, which act as buffers, are desirably added in a suitable amount to achieve a final pH, following adjustment if necessary, of between 5 and 6, especially 5.5.  
30 Suitable concentrations of each component are 0.01-0.4% and 0.01-0.2% (w/w)

respectively, especially 0.31% and 0.2% (w/w) respectively. Dextrose anhydrous is an isotonicity adjusting agent and is added in a suitable amount to achieve isotonicity with fluids of the nasal cavity. Suitable concentrations are between 0.1 and 5% (w/w), especially 5.0% w/w. Phenylethyl alcohol and benzalkonium chloride are preservatives which are preferably added in concentrations between 0.001-1% (v/w) and 0.001-1% (w/w) respectively, especially 0.275% (v/w) and 0.02% (w/w), respectively.

Besides its very good antiallergic properties and the above mentioned reduction in irritancy, the benefits of the invention may include the following:

Surprisingly, we have found that phenylethylalcohol has preservative properties by killing Pseudomonas cepacia (now known as Burkholderia cepacia) by a synergistic effect with benzalkonium chloride. Ps. cepacia is a bacterium which is capable of opportunistic infections such as blood poisoning and due to the bacterium being largely resistant to antibiotics, clinical treatment is complex. Results demonstrating this effect are shown in Figure 7.

A formulation of the present invention may be prepared by the manufacturing process according to the flow diagram shown in Figure 1.

A typical container suitable for a formulation of the present invention may be of the type exemplified in Figures 2 and 3. As a further aspect of the present invention we provide a container comprising a pharmaceutical formulation according to the present invention suitable for delivering it in the form of a nasal spray.

A suitable dosing regime for the formulation of the present invention would be for the patient to inhale deeply subsequent to the nasal cavity being cleared. During inhalation the formulation would be applied to one nostril while the other is

manually compressed. This procedure would then be repeated for the other nostril.

5       Wherein the patient is adult, two inhalations would be administered by the above procedure (100 $\mu$ g beclomethasone dipropionate anhydrate in total) four times each day.

10       Wherein the patient is a child, two inhalations would be administered by the above procedure (100 $\mu$ g beclomethasone dipropionate anhydrate in total) two times each day.

15       It will be appreciated that the above dosing regime should be adjusted according to the patient's age, body weight and/or symptom severity. However, the maximum daily dose should not exceed 16 inhalations for an adult and 8 inhalations for a child. If remission of the nasal symptoms is observed, the dose should be decreased as appropriate.

20       Examples of disease states in which the formulation of the present invention has potentially beneficial anti-inflammatory effects include allergies associated with the nasal cavity, more particularly allergic rhinitis.

25       Thus, according to a further aspect of the invention we provide a pharmaceutical formulation of the present invention for use in the treatment or prophylaxis of allergic rhinitis.

      We also provide a use of a pharmaceutical formulation of the present invention in the manufacture of a medicament for the treatment or prophylaxis of allergic rhinitis.

More specifically, the formulation of the present invention may be illustrated by reference to the following example:

Example 1

5

A solution of propylene glycol (0.3kg) in purified water (23.6kg) is dispersed by mixing at 2000rpm for 5 mins. To this solution, dextrose anhydrate (1.5kg), phenylethyl alcohol (82.5g) and microcrystalline cellulose and carboxymethylcellulose sodium (Avicel RC591; 0.45kg) is then added separately and mixed for a further 10, 5 and 30 mins, respectively. The dispersing is then ceased and the mixture is allowed to stand for 60 mins to hydrate. Dispersion is resumed at 3000rpm for 10 mins and then re-adjusted to 2000rpm.

10

15

Anhydrous disodium hydrogen orthophosphate (93g) is added to purified water (1.8kg) and dissolved by mixing at 3000rpm for 15 mins. This solution is then mixed into the dispersing suspension for 5 mins as is a solution of citric acid, prepared by manually mixing citric acid (0.06kg) with purified water (600g).

20

Glycerol (1.2kg) was heated at  $48^{\circ}\text{C} \pm 2^{\circ}\text{C}$  and polyoxyethylene (20) sorbitan monooleate (Polysorbate 80; 2.1g) is then dissolved in the glycerol. A slurry is then formed by mixing micronised beclomethasone dipropionate anhydrate (30g) with the glycerol and polyoxyethylene (20) sorbitan monooleate solution at 4500rpm at  $48^{\circ}\text{C} \pm 2^{\circ}\text{C}$  for 30 mins. This slurry is then added to the dispersing suspension and mixed for 15 mins.

25

A solution of benzalkonium chloride (50% w/v; 11.82g) is then diluted with purified water (220g), heated to  $35\text{--}40^{\circ}\text{C}$  and then mixed with the drug suspension for 3 mins. Dispersion is then ceased, pH is adjusted to that of an optimum value, typically between 5 and 6, especially 5.5. The drug suspension is then filtered through 100 mesh filters and stored prior to filling into clean

30



bottles. This procedure results in the components being present in the following concentrations:

	Micronised beclomethasone dipropionate anhydrate	0.1% (w/w)
5	Dextrose anhydrous	5.0% (w/w)
	Microcrystalline cellulose	
	and carboxymethylcellulose sodium (Avicel RC591)	1.5% (w/w)
	Phenylethyl alcohol	0.275% (v/w)
	Benzalkonium chloride solution 50% (w/v)	0.04% (v/w)
10	Glycerol	4.0% (w/w)
	Propylene glycol	1.0% (w/w)
	Polyoxyethylene (20) sorbitan monooleate	0.007% (w/w)
	Disodium hydrogen orthophosphate anhydrous	0.31% (w/w)
	Citric acid monohydrate	0.2% (w/w)
15	Purified water	to 100%.

#### Biological Data

The formulation of the present invention, Example 1 (beclomethasone dipropionate anhydrate aqueous nasal spray, hereinafter defined as BANS) which delivers 50 µg BDP in a single spray was tested in a variety of assays to deduce its effect upon nasal symptoms when compared with controls and a prior art formulation (Aldecin™ AQ).

#### 25 1) Effect of BANS on TDI-induced nasal symptoms in sensitised guinea pigs.

Guinea pigs were immunised by 2 x 5 days intranasal application of 10% TDI (toluene 2, 4-diisocyanate) at intervals of 3 weeks. One or two weeks after the final sensitisation, a nasal allergy like response (sneeze, rhinorrhea, nasal obstruction) was provoked by intranasal application of 5% TDI. Drugs were

topically applied 0.5, 1 or 4 hr before the provocation (1 spray each nostril equivalent to 100 µg BDP), however, a control utilised animals sensitised with 5% TDI without drug treatment. Any nasal symptoms were then observed (eg. sneezing, rhinorrhea and nasal obstruction) and scored according to the criteria displayed in Table 1.

Table 1: Criteria used to assign a nasal symptom score for each group

Symptom	Score			
	0	1	2	3
Sneezing	Not observed	1-4	5-11	>12
Watery rhinorrhea	Dry nostril	Snivel observed, but remains within nostril	Snivel leaks from nostril and wets the nasolabial portion, but does not discharge	Snivel drops from the nose
Nasal obstruction	Not observed	Observed	-	-

The sum of the score was regarded as the nasal response of the animal and a 'mean score' value was given for the mean of the scores of each group. The results of this investigation are shown in Figure 4.

2) Effect of BANS on antigen induced nasal vascular permeability in sensitised rats.

Rats were immunised with DNP-As and the animals with 72 hr -PCA titre over x50 were used. Under the anaesthesia, the nasal cavity of the rat was perfused with saline. After the dye (4% pontamine sky blue (Brilliant blue) 5 ml/kg) was intravenously injected, the perfusate was collected for 10 min. Thereafter, the

antigen solution was perfused for 10 min followed by perfusion with saline for further 30 min. The dye concentration of the perfusate collected was determined by absorbance at 616nm. Drugs were topically applied 24hr and 1hr before the provocation (2 sprays at each time equivalent to 100µg BDP). Controls were prepared which utilised antigen challenged sensitised animals without drug treatment (control) and BANS placebo treatment (vehicle). The results of this investigation are shown in Figure 5.

3) Effect of BANS on the increase in intranasal pressure after antigen challenge in sensitised guinea pigs.

Guinea pigs were immunised with OVA by subcutaneous administration in mixture with FCA. The animals with 4 hr-PCA titre over x50 were used. Under the anaesthesia, a Y-shaped cannula was inserted into the trachea of larynx side. One end of the cannula was connected to the transducer to measure intranasal pressure and the other end to air bomb to supply contact flow of the air. After instillation of the antigen solution into the nose, intranasal pressure was measured for 28 min. Drugs were topically applied 24 hr and 1 hr before the provocation (4 sprays at each time equivalent to 200 µg BDP). Controls were prepared which utilised antigen challenged sensitised animals without drug treatment (control) and BANS placebo treatment (vehicle). The results of this investigation are shown in Figure 6.

4) Challenge test of BANS against Ps. Cepacia

Formulations corresponding to BANS and the same formulation containing only 0.02% (w/w) benzalkonium chloride as preservative (i.e. no phenylethyl alcohol) and the same formulation containing only 0.275% (v/v) phenylethylalcohol as preservative (i.e. no benzalkonium chloride) were challenged with an inoculum of Ps cepacia. The results, shown in Figure 7, demonstrate that the combined

preservative is much improved in respect of antimicrobial effectiveness relative to the two preservatives individually in this formulation.

Description of the drawings

5

Figure 1 contains a flow diagram to clearly describe the manufacturing process involved to produce a formulation of the present invention.

10

Figure 2 contains a cross section description of a suitable container for the formulation of the present invention.

Figure 3 contains a cross section diagram of a pump system (Valois VP3/50) with actuator suitable for use in a container such as that described in Figure 2.

15

Figure 4 compares the effect of BANS, Aldecin™ AQ and a control upon TDI-induced nasal symptoms at differing time intervals from drug administration.

20

Figure 5 compares the effect of BANS, Aldecin™ AQ, a vehicle and a control upon antigen induced nasal vascular permeability at a suitable time from drug administration.

25

Figure 6 compares the effect of BANS, Aldecin™ AQ, a vehicle and a control upon the increase in intranasal pressure from 0 to 28 minutes after antigen challenge.

30

Figure 7 shows the results of the challenge test of BANS and the same formulation without one of each of the two preservatives against Ps. cepacia.

Abbreviations

	BANS	beclomethasone dipropionate anhydrate aqueous nasal spray (following Example 1, except where indicated)
5	BDP	beclomethasone dipropionate
	TDI	toluene 2,4-diisocyanate
	FCA	Freund complete adjuvant
	PCA	Passive cutaneous anaphylaxis
	DNP-As	Ascarl's suum extracts conjugated with dinitrophenol (antigen)
10	OVA	Ovalbumin (antigen)
	BKC	Benzalkonium chloride
	PEA	Phenylethyl alcohol

- 15 Throughout the specification and the claims which follow, unless the context requires otherwise, the word 'comprise', and variations such as 'comprises' and 'comprising', will be understood to imply the inclusion of a stated integer or step or group of integers but not to the exclusion of any other integer or step or group of integers or steps.

## C L A I M S

1. A pharmaceutical formulation which comprises an aqueous solution of carboxy methylcellulose sodium, glycerol, propylene glycol and polyoxyethylene (20) sorbitan monooleate, containing suspended therein particulate microcrystalline cellulose and beclomethasone dipropionate anhydrate, characterised in that said aqueous suspension further comprises:
  - Dextrose;
  - Phenylethyl alcohol;
  - Benzalkonium chloride;
  - Disodium hydrogen orthophosphate; and
  - Citric acid.
2. A pharmaceutical formulation according to claim 1 characterised in that it is buffered to a pH of between 5 and 6.
3. A pharmaceutical formulation according to claim 1 characterised in that it is isotonic with fluids of the nasal cavity.
4. A pharmaceutical formulation according to claim 1 having a composition as follows:

	Micronised beclomethasone dipropionate anhydrate	0.1% (w/w)
	Dextrose anhydrous	5.0% (w/w)
25	Microcrystalline cellulose	
	and carboxymethylcellulose sodium (Avicel RC591)	1.5% (w/w)
	Phenylethyl alcohol	0.275% (v/w)
	Benzalkonium chloride solution 50% (w/v)	0.04% (v/w)
	Glycerol	4.0% (w/w)
30	Propylene glycol	1.0% (w/w)

Polyoxyethylene (20) sorbitan monooleate	0.007% (w/w)
Disodium hydrogen orthophosphate anhydrous	0.31% (w/w)
Citric acid monohydrate	0.2% (w/w)
Purified water	to 100%.

5

5. A container comprising a pharmaceutical formulation according to claim 1 suitable for delivering it in the form of a nasal spray.

6. A pharmaceutical formulation according to claim 1 for use in the  
10 treatment or prophylaxis of allergic rhinitis.

7. Use of a pharmaceutical formulation according to claim 1 in the manufacture of a medicament for the treatment or prophylaxis of allergic rhinitis.

8. A method of treatment of allergic rhinitis which comprises administering  
15 to a patient a pharmaceutically acceptable amount of a formulation according to claim 1.

9. A process for preparing a formulation according to claim 1 as herein  
20 before described by reference to the manufacturing flow diagram shown in Figure 1.

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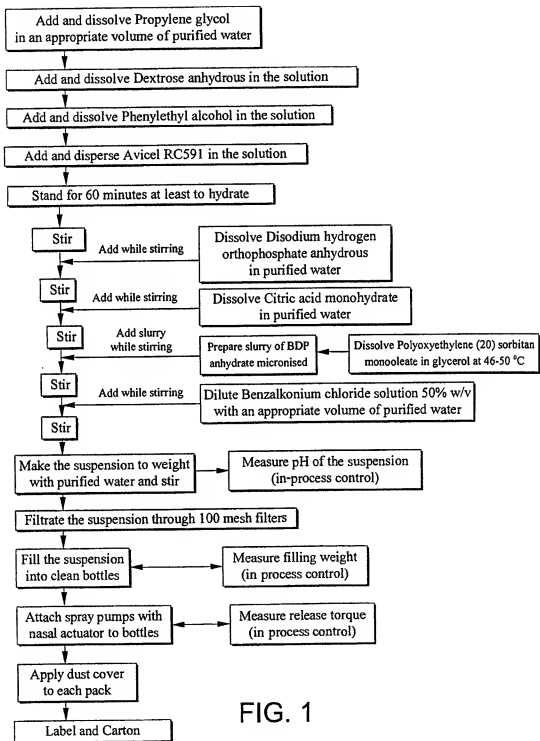


FIG. 1



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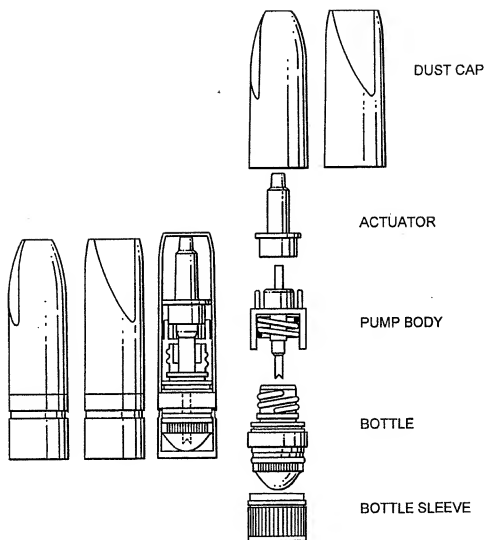


FIG. 2

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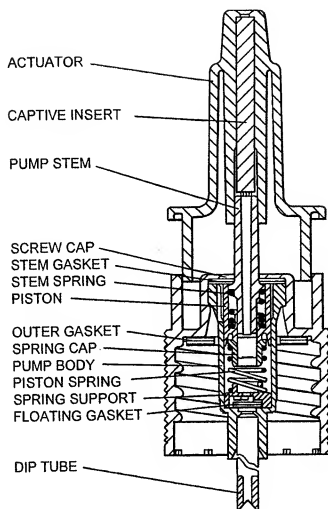


FIG. 3

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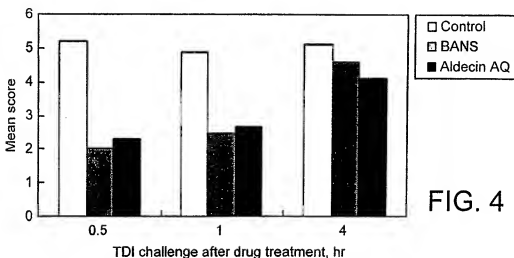
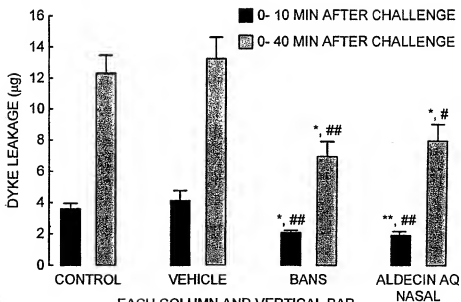


FIG. 4



EACH COLUMN AND VERTICAL BAR  
REPRESENTS THE MEAN  $\pm$  S.E. (n=10)  
\*p<0.05, \*\*p<0.01, VS CONTROL (TUKEY'S TEST)  
#p<0.05, ##p<0.01, VS VEHICLE (TUKEY'S TEST)

FIG. 5

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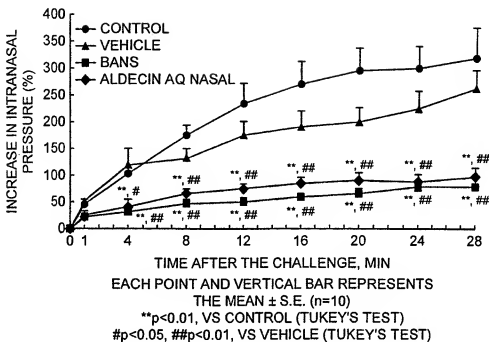


FIG. 6

CHALLENGE TEST OF BANS AGAINST PS. CEPACIA

	LOG <sub>10</sub> REDUCTION*				
	LOG <sub>10</sub> INNOCULUM COUNT	2 DAYS	7 DAYS	14 DAYS	28 DAYS
BKC 0.02% w/w	6.2	0.3	1.0	1.3	1.8
PEA 0.275% v/w	6.2	0.2	0.6	1.7	NR
BKC 0.02% w/w + PEA 0.275% v/w	6.2	NR	NR	NR	NR

\*: LOG<sub>10</sub> REDUCTION = LOG<sub>10</sub> (INNOCULUM COUNT) - LOG<sub>10</sub> (SAMPLE COUNT)  
NR: NO RECOVERY

FIG. 7

## INTERNATIONAL SEARCH REPORT

Intern. Appl. No.  
PCT/JP 00/05200

A. CLASSIFICATION OF SUBJECT MATTER IPC 7 A61K9/08 A61K31/573 A61P37/08		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC 7 A61K		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the International search (name of data base and, where practical, search terms used) EPO-Internal, WPI Data, PAJ, CHEM ABS Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 780 127 A (PROCTER & GAMBLE) 25 June 1997 (1997-06-25) the whole document	1-8
A	& "Remington's pharmaceutical sciences 14th edition" page 1557 -page 1560; table 6	1-8
X	WO 97 46243 A (PROCTER & GAMBLE) 11 December 1997 (1997-12-11) page 2, line 18 - line 36 page 4, line 12 -page 5, line 19 page 7, line 32 -page 8, line 18 page 9 -page 10; examples 1-4 claims 1-3	1-8
A	& "Remington's pharmaceutical sciences 14th edition" page 1557 -page 1560; table 6 --- -/-	1-8
<input checked="" type="checkbox"/> Further documents are listed in the continuation of box C. <input checked="" type="checkbox"/> Patent family members are listed in annex.		
* Special categories of cited documents: 'A' document defining the general state of the art which is not considered to be of particular relevance 'E' earlier document but published on or after the international filing date 'L' document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) 'O' document referring to an oral disclosure, use, exhibition or other means 'P' document published prior to the international filing date but later than the priority date claimed 'T' later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention 'X' document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone 'Y' document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art 'Z' document member of the same patent family		
Date of the actual completion of the international search  18 December 2000		Date of mailing of the international search report  02/01/2001
Name and mailing address of the ISA European Patent Office, P.B. 5816 Patenteaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl Fax (+31-70) 340-3016		Authorized officer  Muller, S

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A	"Aldecin nasal spray"	1-8
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